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Miscellanea

Niridazole in the Treatment of Onchocerciasis

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There is at present no known, non-toxic drug that is effective against both the microfilariae and adult forms of *Onchocerca volvulus*.

The drug most commonly used in the treatment of onchocerciasis is diethylcarbamazine, which in practically all cases kills the microfilariae but leaves the adult worm unaffected, as is suggested by the fact that the skin-snips sooner or later tend to become positive again after treatment. Suramin is effective against the adult worms but is highly toxic and can only be given intravenously, which makes it unsuitable for routine treatment.

In view of these drawbacks, any drug that promises to be of value in the treatment of onchocerciasis is worthy of closer study.

At the end of 1966, I noted that some patients who were being treated at LAMCO Nimba Hospital, Liberia, for *Schistosoma haematobium* infections, but were also suffering from onchocerciasis, had negative skin-snips after completing a course of antischistosomal therapy with niridazole [1].

A review of the literature showed that not much was known about this effect of the drug. Mallén in Mexico had found that niridazole was very effective in vitro against *Onchocerca volvulus,* but ineffective against *Wuchereria bancrofti* and *Loa loa*. In a clinical study, he gave the drug to 9 patients with onchocerciasis for two periods of 7 days each. Most of these patients complained of side effects, mainly in the form of headaches, malaise, nausea and abdominal pain. The nodes, however, became smaller and looser, and in 4 cases they disappeared. Skin-snips revealed a substantial reduction in the number of microfilariae present, but only in one case did the skin-snip become negative. Microscopic study of the nodes revealed thinning of the capsules and massive infiltration with polynuclears. The female worms showed damage to the uterine tubes and regressive changes in the eggs.

Raffier draws rather vague conclusions from his study of 123 cases in the Ivory Coast Republic. He remarks that in some cases skin-snips became negative immediately and that some nodes degenerated or even liquified. He concludes that although niridazole only has a limited effect on *Onchocerca volvulus,* it merits further investigation, perhaps in combination with other drugs.

Duke & Moore in the Cameroons studied only 3 cases. They conclude that Ambilhar has no filariacidal action against either the larval or adult forms of *Onchocerca volvulus*.

The primary aim of the present study was to find out whether niridazole has any effect at all on *Onchocerca volvulus,* and if so whether it is active against the microfilariae only or against both the microfilariae and the adult worms. It is not possible to determine whether a drug is active against the adult worms only, since the already circulating microfilariae are said to have a life-span ranging from 10 months to 5 years.

Although the facilities for carrying out a clinical study of this nature were limited, since in the normal course of events some 10,000 visits are paid to the dispensary each month, which imposes quite a heavy burden on both the medical and laboratory staff, it was found that some extra skin-snips could be managed.

With no pathologist available in Liberia, morphological examinations of the adult worms could not be undertaken.

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[1] Ambilhar, CIBA.

Skin-snips were taken routinely from all patients admitted to the hospital and all applicants for employment, as well as from other patients with cutaneous itch, eye trouble, nodes or other conditions suggestive of onchocerciasis.

The incidence of onchocerciasis in the Nimba area is high. 14.9% of the 3,395 skin-snips tested in the laboratories during 1966 were positive, so there was no difficulty in finding candidates for the trial. Anyone who had positive skin-snips was considered, with the exception of children, outsiders, and old or debilitated patients. The majority of those admitted to the trial were males, but a few females were also included. Since the preliminary analysis showed no difference between the sexes, the results are presented in one group.

In all cases the diagnosis was established by a positive skin-snip. The technique used was as follows: the skin was lifted with a needle, and a piece of epidermis removed with a razor-blade.

It was placed on a slide in a drop of saline and then examined under the microscope for microfilariae. The snips were usually taken from the calves but occasionally, e.g. in patients with a severe localized itch, from other areas.

In some cases the number of microfilariae was recorded, and in some cases more than one snip was taken at the same time, but since this was not always possible, owing to the limited resources already mentioned, no differentiation has been made in the evaluation. Even cases with, for instance, 20 microfilariae in the snip before and only 1 or 2 after treatment are regarded as failures.

Initially, all cases were given niridazole, but later, to afford some means of comparison, one group of patients was given diethylcarbamazine [2] and another a combination of the two drugs.

Drugs and dosage

The dosage of niridazole used was the same as that recommended for the treatment of schistosomiasis, i.e. 25 mg/kg body-weight daily for 7–10 days, patients whose skin-snips were still positive after 7 days being given another 3 days' treatment. In practically all cases, this meant that the actual dosage was one tablet of 500 mg three times daily.

The dosage of diethylcarbamazine recommended in the literature varies greatly. In this study, treatment was started with a dosage of 25 mg twice daily, which was gradually increased to 150 mg three times daily; this dose was then given for two weeks. Patients receiving the combination were given diethylcarbamazine first in the same manner, niridazole being added to the regimen for the last 7 days. To minimize the risk of side effects occurring, all patients treated with diethylcarbamazine were also given an antihistamine during the first few days of treatment.

Side effects

In comparison with the incidence of adverse reactions to niridazole reported among patients with schistosomiasis very few side effects due to Ambilhar were encountered in this series. A few patients complained of nausea or cutaneous itch, which could, as a rule, be relieved with an antihistamine. In three cases psychotic reactions were seen, but all three patients soon recovered after the drug was withdrawn.

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[2] Hetrazan, Lederle.

Results

The results obtained in these cases are shown in the following table. The difficulties associated with the follow-up of these patients will be explained below. Ideally, all patients should be checked at regular intervals, e.g. at the end of treatment and after 1, 2, 3 and 6 months and possibly even later. Since this was not possible, snips were taken from these patients whenever they appeared at the dispensary or hospital. Some have therefore only been seen once after treatment, whereas other were checked several times at various intervals. This again has made it difficult to summarize the results.

	Negative					*Positive*			
	At end of treatment: not seen later	At end of treatment and at last check after 1-2 months	3-5 months	6 months	Total neg.	At end of treatment	After 1-6 months	Total pos.	Percentage known to have been pos. within 6 months
Niridazole *95* cases	35	5	3	22	*65*	15	15	*30*	*31.6%*
Diethyl-carbamazine *41* cases	6	6	5	17	*34*	0	7	*7*	*17.1%*
Niridazole + diethyl-carbamazine *63* cases	29	11	9	6	*55*	2	6	*8*	*12.7%*

Discussion

Scientific trials in developing countries are complicated by several factors. Although the material may seem abundant there are many problems involved, of which perhaps the most difficult is to ensure that the patients really do take the treatment. In our dispensary, we found it necessary to have the patients come daily for their supply of the drug. This is, of course, inconvenient for the patient, but there does not seem to be any other way of making certain, or at least reasonably certain, that the treatment is taken. The problem does not arise, if the patient is hospitalized, but this was only rarely the case in this trial. Even if the patients do take the drug, it is no easy matter to get them to report for follow-up controls, since the majority are virtually illiterate and have only a vague idea of time. The chances of having regular checkups made are therefore slight, and to carry out a double-blind test under these circumstances is quite impossible.

Apart from these general difficulties, there are specific problems associated with onchocerciasis. A positive skin-snip may indicate the persistance of surviving microfilariae, though the adult worm may be dead. A negative snip may be due to the absence of microfilariae from this particular area of the body at the time. It would be most interesting to follow up a few untreated cases in which snips are

taken regularly from different parts of the body, but although the snip in itself is hardly painful, it might be difficult to find suitable candidates.

The problem of reinfection must also be taken into account. It is difficult to estimate how soon after reinfection a patient may harbour adult worms capable of producing new microfilariae. Not much seems to be known about this question but CALLOT and HELLWY have discovered nodules in children of 3 months of age. Lacking more precise knowledge, I have put the limit at 6 months. If it were possible to follow up all cases for a few years, the incidence of late positive skin-snips in the various groups might give a clue to this problem.

On the basis of the evidence obtained by other investigators and the results presented here, however unreliable they may be, it is not possible to draw any definitive conclusions regarding the effect of niridazole in onchocerciasis. However, the drug does appear to exert a certain therapeutic activity in this condition and further investigations to establish its value in the treatment of onchocerciasis would undoubtedly be justified.

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